REMARKS

Claim Amendments

Claims 1, 2, 10, 16, 17, 18, 19, 21 and 22 have been amended. Support for the amendments can be found throughout the specification, see, e.g., US2001/0036457 (published application), ¶¶ 59-66, and in the previously submitted claims. The amendments do not add any new matter.

35 U.S.C. §112, ¶2

The Examiner has rejected claim 22 as allegedly indefinite, stating that the meaning of "present" as used in the claim is unclear.

Applicants respectfully disagree. However, in order to expedite prosecution, Applicants have amended claim 22 to more clearly define the invention; the claim has not been narrowed by virtue of this amendment. Claim 22, as amended, is clear and definite. Accordingly, Applicants respectfully request that the Examiner reconsider and withdraw this indefiniteness rejection.

35 U.S.C. §112, ¶1

Written Description

The Examiner has rejected claims 1, 2, 4 7-10 and 16-29 as allegedly failing to comply with the written description requirement. With respect to claims 1, 4, 10 and 16 (and the claims dependent thereon), the Examiner alleges that the specification does not adequately describe a "circulating tumor antigen." With respect to claims 23 and 29 (and the claims dependent thereon), the Examiner alleges that antigens sialyl-LeA, sialyl-LeX, PSA, CEA and CA50 were not described in the originally filed disclosure.

Applicants respectfully submit that the amendments to the claims obviate this rejection. Applicants respectfully request that the Examiner reconsider and withdraw these written description rejections.

Enablement

The Examiner objects to claim 1, 2, 4, 7-10 and 16-29 as allegedly failing to meet the enablement requirement. The Examiner states that the specification does not enable "a method of inhibiting growth of cancer cells and eliciting a therapeutic immune response in a patient

comprising administering a non-radiolabeled antibody which binds to a first epitope on the tumor associated antigen and elicits an effective immune response against a second epitope on the antigen."

The Examiner states that the specification contemplates that binding of an antibody to a tumor associated antigen ("TAA") may change the conformation of the antigen sufficiently to provide access to another previously unrecognizable epitope on the antigen, but fails to disclose "the characteristics of the first epitope of the tumor associated antigen relative to the second epitope of the tumor antigen, or the location of the antibody complex of the tumor associated antigen which would cause the re-conforming of the tumor associated antigen and recognition of the second epitope necessary to expose a previously unrecognizable epitope on said antigen so that one of skill in the art could reliably elicit this effect given any tumor antigen." The Examiner points out that a person of skill would have no guarantee that the binding of an antibody to an antigen will produce a conformational change in the antigen. Further, the Examiner states that the specification does not disclose the "criteria for the 'binding agent' which would result in a re-conforming of the tumor antigen after binding." The Examiner concludes that "one of skill in the art would be subject to undue experimentation without reasonable expectation of success in order to practice the claimed invention."

Applicants traverse. The specification only needs to teach how to practice ***the claimed invention*** without undue experimentation. The claims do not recite that the binding of the antibody to a TAA results in a conformational change of the TAA. Nor is this essentially required for the claimed invention to work (see ¶ 60, stating that once an antibody binds to an antigen, either the conformation of the antigen is altered or the antigen is processed and/or delivered differently so that it is recognized by the host's immune system). Accordingly, Applicants do not need to describe the structural requirements of the TAA and/or of the antibody which would result in an altered conformation of the TAA. Rather, the claims require the antibody to bind to a first epitope on the TAA, thereby generating an immune response to a second epitope on the antigen, and eliciting a host immune response against cancer cells producing the antigen. Each of these aspects is adequately disclosed in the specification to enable a person of skill in the art to practice the invention.

Antibodies which recognize tumor antigens can be obtained using no more than routine experimentation. Further, a person of skill in the art can determine whether the administration of an antibody which recognizes a first epitope on an antigen generates an immune response against

a second epitope on the antigen using no more than routine experimentation. In this regard, Example 1 of the specification exemplifies one method of determining whether the administration of an antibody which recognizes a first epitope on an antigen generates an immune response against a second epitope on the antigen. Finally, a person of skill in the art can determine whether an antibody elicits a host immune response against cancer cells producing the antigen using no more than routine experimentation. Accordingly, the claims are enabled throughout their scope.

In view of the above arguments, Applicants respectfully request that the Examiner reconsider and withdraw this enablement rejection.

35 U.S.C. §103

Rejection in view of Wagner and Madilayakan

The Examiner has rejected claims 1, 2, 4, 8, 10, 16-24 and 29 as obvious over *Wagner* in view of *Madilayakan*. *Wagner* and *Madilayakan* disclose the administration of radiolabeled anti-CA125 antibodies to ovarian cancer patients for diagnostic purposes. According to the Examiner, *Madilayakan* discloses that a statistically significant number of patients who survived more than two years had induction of the anti-idiotypic network; and *Wagner* discloses that the survival rates for patients who developed anti-idiotypic antibodies is greater than the survival rates of patients being treated with surgery and chemotherapy. The Examiner states that *Wagner* postulated that the effect was not due to the radiolabel in the antibody because the amount of radioactivity was very low. According to the Examiner a person of ordinary skill in the art would have been motivated to administer non-radiolabeled B43.13 antibodies to patients having soluble CA125 levels in their blood "by the teachings of *Madilayakan* on the correlation between levels of CA125 in the blood, the induction of the anti-idiotypic network as evidenced by AB2 and the prolonged survival of said patients, in addition to the teachings of *Wagner* who suggest that the induction of the anti-idiotypic network was responsible for the effects seen with the radiolabeled B43.13 antibody which did not have enough specificity to account for the direct killing of tumor cells by radioactivity."

Applicants respectfully traverse. Neither reference discloses or suggests the use of a non-radiolabeled antibody which binds to first epitope on a TAA and generates an immune response to a ***second epitope*** on the antigen, as required by claims 1, 2, 4, 8, 10, 16-24 and 29. *Wagner* and *Madilayakan* only refer to the induction of the idiotypic network in patients

receiving anti-CA125 antibodies. Thus, at best, *Wagner* and *Madilayakan* teach that the administered anti-CA125 antibodies (Ab1) induce the production of anti-idiotypic antibodies (Ab2) and anti-anti-idiotypic antibodies (Ab3). Anti-idiotypic antibodies (Ab2) bind to the administered antibody and constitute the "internal image" of the original antigen. Anti-anti-idiotypic antibodies (Ab3) bind to the ***same epitope*** that is bound by the administered antibody rather than to a second epitope. (See, e.g., specification, Example 1, stating that Ab3 antibodies generated under this pathway would bind and be inhibited only by MAb-B43.13, because the B43.13 epitope is the only epitope present.) Accordingly, neither reference discloses or suggests that the administered antibodies could elicit a response against a second epitope on the antigen.

Further, neither *Wagner* nor *Madilayakan* administered the antibodies as therapeutic agents. Moreover, neither administered the antibodies as part of a controlled study. Thus, any observations made in these references regarding the therapeutic benefit of the antibodies were based solely on retrospective analysis of limited and complex data from patients who were exposed to the antibody in different ways and who were likely receiving other treatments such as chemotherapy. As such, a person of ordinary skill in the art could not reasonably expected that the administered antibodies had any therapeutic effect. (See, e.g., *Madilayakan*, page 202 stating: "However, this being a retrospective analysis of the serum from these patients, it is difficult to suggest a singular correlation between survival and idiotype induction as some of these patients were also receiving a variety of other conventional treatment.")

In view of the above arguments, Applicants respectfully request that the Examiner reconsider and withdraw this obviousness rejection over *Wagner* and *Madilayakan*.

Rejection in view of Chang, Simitselk, Golumbek and Jacobs

The Examiner has rejected claims 1, 2, 4, 8, 10, 16-24 and 29 over *Chang* in view of *Simitsek*, *Golumbek* and *Jacobs*. *Chang* allegedly teaches a method of enhancing an immune response to an antigen *in vivo* comprising administering an antigen-antibody complex formed with a molar excess of the antibody. *Simitsek* allegedly discloses that the processing of T-cell determinants in an antigen can be modulated by the presence of a bound antibody and that determinants which are physically separated from the antibody have an increase likelihood of being captured for class II MHC presentation relative to the determinant that is directly bound by the antibody. Neither *Chang* nor *Simitsek* disclose or suggest anything relating to tumor antigens, and in particular the specific tumor antigens recited in the amended claims. *Golumbek*

allegedly teaches that the goal of immunotherapy is to break tolerance to tumor specific antigens. *Jacobs* allegedly teaches that CA125, CA19.9 and CA15.3 are TAA that are present on the surface of cancer cells, and shed into the blood of cancer patients.

Applicants respectfully traverse. At the outset, Applicants submit that none of the cited references teaches a method for inhibiting the growth of cancer cells comprising administering an antibody that binds to a first epitope on a TAA and generates an immune response against a second epitope of the TAA, wherein the TAA is CA19.9, CA15.3 or CA125. *Chang* only discloses administering a ***complex*** of antibody and a ***foreign antigen*** (rather than a TAA). *Simitsek* only discloses that antibodies can modulate the presentation of various T cell determinants in a ***foreign antigen*** *in vitro*. *Golumbek* only discloses a way of modifying cells genetically so to alter the presentation of TAA. *Golumbek* does not disclose or suggest breaking the tolerance to self-antigens by administering an antibody that binds to a first epitope of a TAA and elicits a response against a second epitope of the TAA. *Jacobs* only teaches that certain TAA are shed into the circulation. *Jacobs* does not disclose or suggest breaking the tolerance to self-antigens by administering an antibody that binds to a first epitope of a TAA and elicits a response against a second epitope of the TAA.

Further, Applicants respectfully submit that a person of ordinary skill in the art would not have been motivated to combine the teachings of the above cited references to arrive at the claimed invention. First, *Chang* and *Simitsek* relate to foreign antigens while *Golumbek* and *Jacobs* relate to TAAs. The issues relating to the elicitation of an immune response against TAAs such as CA19.9, CA15.3 and CA125, which are self-antigens, are inherently different from the issues relating to the elicitation of an immune response against foreign antigens. For example, unlike foreign antigens, TAAs are not generally recognized by the immune system. This may be due to the fact that the host usually develops tolerance against TAAs and/or the tumor cells develop ways to evade the immune system or elicitation of an immune response. Accordingly, recognizing and eliciting an immune response against foreign antigens is generally a much simpler process than recognizing and eliciting an immune response against TAAs. Second, nothing in *Chang* or *Simitsek* suggests the use of the claimed methods with respect to the specific antigens recited in the amended claims.

At the time the invention was made, the art was still searching for effective ways of inducing immune responses against TAA, a much bigger challenge than inducing immune responses to foreign antigens. A major obstacle in using TAAs to elicit an immune response is

that the host is generally tolerant to TAAs. Tumors arise from self, and express self antigens. As summarized in *Paul* (Exhibit A), TAAs often have various mechanisms for escaping or failing to elicit an immune response. For example, there are pathways for the deletion of auto-reactive B cells, associated antibodies and auto-reactive T cells. In addition, tumor cells can release factors that could inhibit or kill T cells directly. At the time that the invention was made, the tolerance against self antigens was a well-recognized obstacle for the development of effective immune responses against tumor antigens. *See, e.g.,* Sotomayor et al., "Tolerance and Cancer: A Critical Issue in Tumor Immunology," *Crit. Rev. Oncog.* 7(5-6):433-456 (1996) (Exhibit B) emphasizing that a better identification and understanding of the factors involved in tumor-induced tolerance is required for the development of novel cancer immunotherapies. A review article published two years after the earliest filing date of the present application, Antonia et al., "Immunologic nonresponsiveness to tumors," *Crit. Rev. Oncog.* 1998;9(1):35-41 (Exhibit C) ("*Antonia*"), notes that T cells are generally not effective in rejecting tumors and that T cells are often tolerant to TAAs. *Antonia* further states that "tumor cells can acquire attributes that interfere with an immune response including down-regulation of MHC molecules or other molecules involved in antigen processing." These references demonstrate that, at the time the invention was made, the art had not found a safe and effective way to break the tolerance that is generally associated with TAAs.

In view of the fact that foreign antigens and tumor antigens are processed and/or presented differently and do not necessarily elicit the same type of immune responses through the same mechanisms, there would have been no motivation to combine the teachings of references related to the recognition of TAAs with the teachings of references related to the recognition of foreign antigens.

Moreover, as discussed above, even if the references were combined, the combination of references still would not teach all of the limitations of the pending claims. As discussed above, none of the references teach or suggest a method for inhibiting the growth of cancer cells comprising administering an antibody that binds to a first epitope on a TAA and generates an immune response against a second epitope of the TAA.

Finally, even assuming *arguendo* that a person of ordinary skill in the art would have been motivated to combine the teachings of these two sets of references, a person of ordinary skill in the art would not have had any reasonable expectation that the use of an antigen/antibody complex would break the immune tolerance that is generally associated with the recognition of TAAs. None

of the cited references (whether taken independently or combined with each other) suggest or provide any evidence that an antibody to a TAA could render the TAA immunogenic. Instead, at the time that the application was filed, the art recognized that it was very difficult to induce an immune response against a TAA because the hosts have various mechanisms or pathways to limit their immune responses against self antigens.

In view of the above arguments, Applicants respectfully request that the Examiner reconsider and withdraw this obviousness rejection over *Chang*, *Simitselk*, *Golumbek* and *Jacobs*.

35 U.S.C. § 102(b)

Rejections in view of Nudelman and Fagnani

The Examiner has rejected claims 16, 17, 18, 27, 28 and 29 as been anticipated by either *Nudelman* (U.S. Patent No. 5,240,833) or *Fagnani* (EP 315456). *Nudelman* allegedly discloses a therapeutic composition comprising antibodies against sialyl-LeA and sialyl-LeX and physiologically acceptable diluents, in an amount ranging from 1-5 micrograms per body weight. *Fagnani* allegedly discloses a therapeutic composition comprising an antibody which binds to CEA or PSA complexed with a dextran, wherein said composition comprises 0.01 to 200 mg of the conjugate, which according to the examiner meets the limitations of claims 27-28 when only the immunoglobulin portion of the conjugate is accounted for in terms of weight.

Applicants respectfully submit that the claim amendments obviate this rejection. Neither *Nudelman* nor *Fagnani* disclose or suggest the use of an antibody against CA19.9, CA15.3 or CA125 as recited by the amended claims. Accordingly, Applicants request that the Examiner reconsider and withdraw this anticipation rejection.

Rejections in view of Unger and Kokulus

The Examiner has rejected claims 16, 17, 18 and 29 as been anticipated by either *Unger* (U.S. Patent No. 6,088,613) or *Kokulus* (U.S. Patent No. 5,807,978). *Unger* allegedly discloses a therapeutic composition comprising an imaging agent and anti-CA15.3 antibodies. *Kokulus* allegedly discloses a therapeutic composition comprising an anti-PSA antibody conjugated to paramagnetic probes for *in vivo* detection.

Applicants respectfully traverse. In order for a reference to be anticipatory, the reference must disclose each and every element of the claim. *Kokulus* does not disclose or suggest the use

of an antibody against CA19.9, CA15.3 or CA125 as recited by the amended claims. *Unger* does not disclose or suggest the use of an antibody which binds to a first epitope on a TAA and elicits an effective host immune response against a second epitope as required by claims 16-18 and 29. Accordingly, neither *Unger* nor *Kokulus* anticipates claims 16-18 and 29. Applicants respectfully request that the Examiner reconsider and withdraw this anticipation rejection.

CONCLUDING REMARKS

In view of the above amendment, applicant believes the pending application is in condition for allowance.

Applicant believes no fee, other than the fee associated with the accompanying petition for a three-month extension of time, is due with this response. However, if an additional fee is due, please charge our Deposit Account No. 18-1945, under Order No. AREX-P02-005, from which the undersigned is authorized to draw.

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Respectfully submitted,

By _____

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Attachments:
Exhibit A
Exhibit B
Exhibit C